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Chemotherapy treatment for breast cancer can cause psychological distress on a daily basis and intense distress on treatment days. Previous research raises the possibility that this stress may affect patients' physical health. Our ongoing longitudinal study investigates the hypothesis that stress contributes to the increased risk of infectious disease in women (N = 200) receiving myelotoxic chemotherapy for breast cancer. Study objectives are: 1) To investigate the effects of major life events prior to treatment on neutropenia and infectious disease during and after chemotherapy in 200 women with breast cancer; 2) To examine the effects of psychological stress associated with individual chemotherapy treatments on neutropenia and infectious disease; and, 3) To explore the relations between episodes of infectious disease and daily psychological stresses.

During this first year of the four-year study, we initiated and implemented the research plan. As expected at this early stage of a prospective, longitudinal study, additional data is required to address the specific aims. However, the available data allowed the investigation of an ancillary issue directly relevant to the overall goal of the research - predictors of distress associated with treatment. Results indicate the involvement of classical conditioning mechanisms, suggesting the complexity of possible interactions between psychobehavioral and biological processes.

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5. INTRODUCTION

5.1 Overview

Neutropenia and the associated risk of infection in women receiving cytotoxic chemotherapy remains a significant clinical problem in the treatment of breast cancer. Dose intensification, which would increase the antineoplastic efficacy of standard chemotherapy treatments, is constrained by the increased risk of infection as the myelotoxic side effects become more severe. It is therefore important to consider factors that may contribute to the risk of infection in these patients. One such factor is suggested by accumulating evidence that psychological stress increases the risk of infection in otherwise healthy individuals. The ongoing research is the first to examine the effects of psychological stress on neutropenia and infectious disease in patients receiving chemotherapy. Greater understanding of the processes involved in the effects of psychological stress on neutropenia and infectious disease in these patients may lead to novel therapeutic approaches ranging from psychological interventions to pharmacologic manipulation of neuroendocrine influences on the immune system.

During this first year of the planned four-year study, our initial goal was to develop the research infrastructure (e.g., hire study personnel) and establish collaborative arrangements for recruitment and assessment of study subjects. We then focused on the initiation and implementation of the research plan as described in the grant application. As expected at this early stage of a prospective, longitudinal study, additional data is required before there is sufficient statistical power for the specific aims to be appropriately addressed. On the other hand, data was sufficient to allow the investigation of an ancillary issue that is directly relevant to the overall goal of the research. Fifty subjects were recruited for this study.

This Annual Report on Grant Number DAMD17-94-J-4141, "Psychological Stress, Neutropenia, and Infectious Disease in Patients Receiving Chemotherapy Treatment for Breast Cancer," focuses on this first study to be completed with the support of the above referenced grant.

5.2 The Nature of the Problem

Patients receiving chemotherapy for cancer experience considerable emotional distress, as documented in numerous clinical reports (1-5). Although many possible sources of distress have been examined in these studies, little attention has been paid to the possibility that these sources may vary with the timing of the assessment in relation to chemotherapy administration. In most previous studies, no distinction was made between distress experienced after treatment infusions (posttreatment distress) and distress experienced in the clinic before infusions (anticipatory distress). This

distinction may have heuristic value because there may be different sources of distress during these two periods.

During the posttreatment period, patients may experience a variety of aversive side effects (e.g., pain, fatigue, nausea) (6). Considerable research suggests that patients who experience more side effects have higher levels of emotional distress during the posttreatment period (7,8). During the pretreatment period, however, distress may occur even in the absence of treatment side effects. Indeed, distress has been found to be most severe prior to patients' first infusion of chemotherapy (i.e., prior to any experience with chemotherapy) (5,9). High levels of distress prior to the first infusion of chemotherapy have been linked to trait anxiety, an individual's propensity to experience anxiety in threatening situations (10), as well as to patients' expectations of experiencing aversive side effects (9). At subsequent infusions, patients' prior experience of aversive side effects and emotional distress may also contribute to anticipatory distress. Based on their experiences of these aversive side effects, patients may become distressed due to their expectations of having similar reactions again. Patients' prior experiences of posttreatment distress may result in the development of classically conditioned distress at subsequent infusions.

The role of classical conditioning in the development of anticipatory reactions to chemotherapy has been most extensively studied with regard to anticipatory nausea and vomiting (ANV) (11). Numerous clinical studies indicate that ANV develops when the sights, smells, and sounds in the clinic environment (putative conditioned stimuli) are paired with the administration of chemotherapy (unconditioned stimulus) that elicits posttreatment nausea and vomiting (unconditioned response). After one or more pairings, exposure to these clinic cues alone (e.g., in the clinic, before chemotherapy is administered) is sufficient to elicit nausea and/or vomiting (conditioned response) (12-14).

Analogous to conditioned nausea and vomiting, conditioned emotional distress has been hypothesized to develop when clinic cues are paired with chemotherapy that elicits posttreatment emotional distress (putative unconditioned response) (2,5,9). To date, two lines of evidence support this hypothesis. First, consistent with the view that clinic cues function as conditioned stimuli, patients' distress levels have been found to increase markedly upon their return to the clinic environment where they had received treatment (5,15). Second, consistent with the view that posttreatment distress functions as an unconditioned response, the presence of distress after an infusion has been found to predict the occurrence of anticipatory distress at the next infusion, regardless of the number of other side effects reported (9). Although the results of these studies are consistent with a conditioning explanation, no study has yet examined the importance of conditioning, relative to other factors, in predicting the severity of anticipatory distress in chemotherapy patients.

6. BODY

6.1 Purpose of the Present Work

The primary aim of the present study was to examine the contribution of patients' levels of posttreatment distress (intensity of the unconditioned response) to their subsequent levels of anticipatory distress. This contribution of posttreatment distress was statistically compared to that of the following nonconditioned sources of anticipatory distress: 1) proneness toward experiencing anxiety in threatening situations (trait anxiety); 2) apprehension about chemotherapy (operationally defined as the level of emotional distress before the first infusion); and 3) the extent of aversive treatment-related symptomatology (total number of side effects other than emotional distress).

We hypothesized that posttreatment distress (putative unconditioned response) would be a more important predictor of anticipatory distress as patients underwent more treatment infusions (putative conditioning trials). We also hypothesized that the predictor variables would both directly and indirectly (by influencing one another) influence the intensity of patients' anticipatory distress.

6.2 Experimental Methods

6.21 Subjects

Fifty women scheduled to receive intravenous adjuvant chemotherapy treatment for breast cancer who met the following criteria were included in the present sample: 1) diagnosed with Stage I or II breast cancer, status post radical, modified radical, or segmental mastectomy; 2) Karnofsky performance status over 70; 3) no previous chemotherapy treatment; 4) not scheduled to receive radiation during the course of chemotherapy; 5) 18 years of age or older; 6) not currently pregnant; 7) no current or previous neurological or psychiatric disorders; 8) no concurrent serious illness; 9) English speaking; 10) no hearing impairment; 11) not scheduled for oral chemotherapy; and 12) complete data collected for eight infusions.

Patients ranged in age from 28 to 74 years with a mean age of 48 years (s.d. = 10.3). The sample was predominately white (82%), married (69.4%), and well-educated, with 59% having at least a college degree. Most women (56.2%) were working at the start of chemotherapy, while 23% were not working (students, retirees, homemakers) and 20.8% were on leave from employment.

A review of patients' medical records indicated that they were treated with the following standard combinations of chemotherapy agents: (1) CMF (cyclophosphamide

[C] [600 mg/M^2], methotrexate [M] [40 mg/M^2], and 5-fluorouracil [F] [600 mg/M^2]) I.V. q 21/28 d (n = 38); (2) Adriamycin (75 mg/M^2) I.V. q 21 d followed by CMF as above (n = 10); (3) Adriamycin (75 mg/M^2) I.V. q 21 d (n = 1); or (4) CMF as above followed by CAF (C [500 mg/M^2], adriamycin [50 mg/M^2], and F [600 mg/M^2]) I.V. q 28 d (n = 1). Patients received a standard regimen of I.V. antiemetic medications at each infusion, including dexamethasone (10 - 40 mg) and lorazepam (0.5 - 2.0 mg). This regimen was modified as clinically necessary on an individual basis by each patient's attending oncologist with one or more of the following: prochlorperazine (10 mg), metoclopramide hydrochloride (40 - 100 mg), ondansetron (0.15 mg/kg), or diphenhydramine hydrochloride (25 - 50 mg). Repeated measures analysis of variance revealed that antiemetic doses did not vary over the course of treatment (p's $\geq$.26).

6.22 Procedures

As in our previous research, patients completed study measures (described in detail below) in the clinic waiting area before each treatment infusion. Patients were also contacted by telephone four to seven days after each infusion to assess the presence of chemotherapy-related side effects, including distress (see below). In addition, patients completed a demographic data form and a measure of trait anxiety. Assessment instruments are described below.

Trait Anxiety: Patients completed the Taylor Manifest Anxiety Scale (TMAS) (18) at home between their second and third chemotherapy infusions. Because trait anxiety, as measured by the TMAS, has been demonstrated to be a stable trait (three-week test-retest reliability, r = .89; five-month test-retest reliability, r = .82 (18)), patients completed this questionnaire at home to reduce the time required for clinic assessments.

Pretreatment assessments: During each pretreatment infusion assessment, patients reported the intensity of emotional upset and nausea on 10-centimeter visual analog scales (VAS), as previously described (16). Separate VAS for emotional upset and nausea were completed for the following time points: last night; this morning; and right now. Data from these time points were combined (mean) with the measure of distress in the treatment room (see below) to define patients' levels of anticipatory distress based on evidence indicating high intercorrelations (r = .21 to .96).

Posttreatment assessments: During each posttreatment infusion telephone assessment, patients were asked to report on the presence or absence of 12 common side effects, as previously described (16). Patients also reported the intensity of posttreatment emotional upset and nausea (0-100) in the 24 hours after chemotherapy administration and provided a retrospective assessment of the presence and intensity (0-100) of emotional upset and nausea in the treatment room immediately before

chemotherapy administration. The side effects assessed were: chills, sleep problems, diarrhea, weakness, fatigue, hair loss, vomiting, taste change, change in appetite, skin itching, and pain.

6.23 Data analytic approaches

This study was designed to test two hypotheses. First, we predicted that posttreatment distress (putative unconditioned response) would become a more important predictor of subsequent anticipatory distress as patients received more chemotherapy infusions (putative conditioning trials). To test this hypothesis, we conducted a series of stepwise multiple regression analyses to examine the contribution of each of the predictor variables to the intensity of patients' anticipatory distress at the second through the eighth infusions. Second, we proposed that some predictor variables might have an indirect influence on anticipatory distress through their effects on more proximal variables. Specifically, we hypothesized that trait anxiety might influence patients' apprehension about chemotherapy (distress before infusion one), which, in turn, might influence subsequent anticipatory distress. Similarly, distress before infusion one might influence both posttreatment distress and the number of posttreatment side effects. Each of these variables, in turn, might independently influence subsequent anticipatory distress. Our proposed causal model is graphically depicted in Figure 1. To explore these proposed causal relations among the variables under study, we performed a path analysis (19) of the sources of anticipatory distress at the eighth infusion.

6.3 Results

Anticipatory Distress: Distress levels assessed during the pretreatment period were highest before the first infusion 36.8 $\pm$ 26.7 (mean $\pm$ s.d.), and ranged from 24.2 $\pm$ 21.5 to 30.2 $\pm$ 24.3 across subsequent infusions. At each infusion, the vast majority of women (ranging from 94 - 100%) had some anticipatory distress (i.e., $>$ 0).

Predictors of Anticipatory Distress Across Infusions: Preliminary analyses were conducted to determine whether demographic variables (i.e., age, race, education, marital status, employment status) were related to patients' distress levels prior to treatment infusions. The only variable found to be associated with anticipatory distress was age, which was correlated at only one of the eight infusions. Confirming the importance of trait anxiety as a predictor of distress before the first treatment infusion (9), a significant correlation was found between these two variables ($r = .53$, $p = .001$).

To examine the sources of anticipatory distress across subsequent infusions (i.e., infusions 2 - 8), separate stepwise multiple regression equations were computed to identify which variables were related to the intensity of anticipatory distress before each infusion. Four variables previously reported to be related to anticipatory distress (trait anxiety, distress intensity before the first infusion, number of posttreatment side effects after the prior infusion, and level of posttreatment distress after the prior infusion) were included as predictors in these analyses. Following stepwise procedures, the predictor accounting for the most variability in anticipatory distress scores was allowed to enter each analysis on the first step, followed by the predictor accounting for the most remaining variability on step 2, and so on, until no remaining variable made a significant ($p \leq .05$) contribution. Thus, the variable identified in step 1 (see Table) is the strongest predictor of anticipatory distress (i.e., accounted for the most variability) and is followed by the variables accounting for the most remaining variability on subsequent steps.

Consistent with the conditioning hypothesis, posttreatment distress (putative unconditioned response) was significantly related to anticipatory distress at the fourth infusion and became the strongest predictor by the sixth infusion (see Table). Distress before infusion one (apprehension about chemotherapy) was the strongest predictor of anticipatory distress before infusion two, and remained significant at all subsequent infusions. The number of posttreatment side effects was a significant predictor at only two infusions (three and five). Trait anxiety was not a significant predictor at any infusion after the first.

Table 1: Significant Predictors of Anticipatory Distress at Infusions 2-8

	Infusion 2	Infusion 3	Infusion 4	Infusion 5	Infusion 6	Infusion 7	Infusion 8
Step 1	Distress Before Infusion 1 $R^2 = .44^{***}$	Posttreatment Side Effects $R^2 = .19^{**}$	Posttreatment Distress $R^2 = .37^{***}$	Distress Before Infusion 1 $R^2 = .30^{***}$	Posttreatment Distress $R^2 = .41^{***}$	Posttreatment Distress $R^2 = .24^{***}$	Posttreatment Distress $R^2 = .34^{***}$
Step 2		Distress Before Infusion 1 $R^2 = .07^{*}$	Distress Before Infusion 1 $R^2 = .11^{**}$	Posttreatment Distress $R^2 = .11^{**}$	Distress Before Infusion 1 $R^2 = .16^{***}$	Distress Before Infusion 1 $R^2 = .08^{*}$	Distress Before Infusion 1 $R^2 = .13^{**}$
Step 3				Posttreatment Side Effects $R^2 = .05^{*}$			

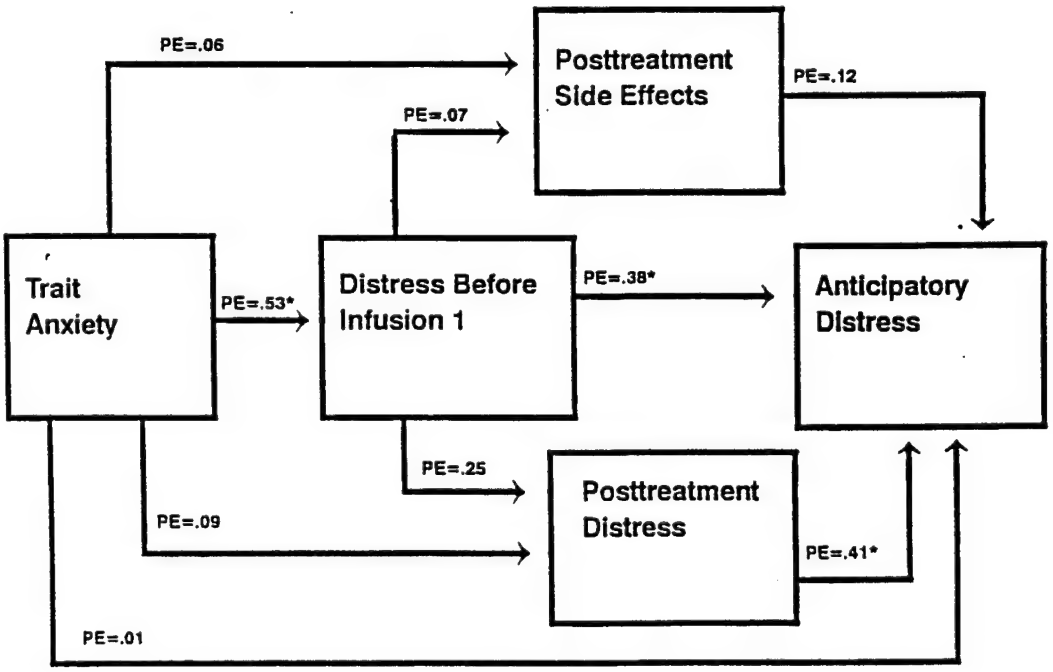
* $p < .05$

** $p < .01$

*** $p < .001$

Analysis of Direct and Indirect Predictors of Anticipatory Distress: Although the previous results indicate that posttreatment distress is the strongest predictor of anticipatory distress at infusions six through eight, the stepwise regression approach does not address the possibility that the predictors may have both direct and indirect relations with anticipatory distress. Direct relations would be evident if the predictor accounted for variability in anticipatory distress independent of other predictors. Indirect relations would be evident if the predictor accounted for variability in other predictors which, in turn, had direct relations with anticipatory distress. To examine the direct and indirect relations between the predictor variables and anticipatory distress before the eighth infusion, we conducted a classic path analysis (19). This analysis tested the existence of the proposed paths relating the predictor variables to each other and to anticipatory distress and estimated their associative strength.

The model and path coefficients are presented in the Figure. Trait anxiety was found to be neither directly related to anticipatory distress nor indirectly related via posttreatment side effects or posttreatment distress. However, trait anxiety did have an indirect effect on anticipatory distress through its influence on anxiety before infusion one. Patients higher in trait anxiety reported higher distress before the first infusion, and as shown in the Figure, distress before the first infusion had a direct effect on anticipatory distress. Consistent with the conditioning hypothesis, posttreatment distress was also directly related to anticipatory distress, such that higher levels of posttreatment distress were predictive of greater anticipatory distress.



Although the stepwise regression and the path analysis suggest that posttreatment distress accounts for significant variability in anticipatory distress, it is important to consider the possibility that this effect may have reflected the shared variance of posttreatment distress and posttreatment side effects, which were significantly correlated ($p < .001$). In order to confirm the unique contribution of posttreatment distress after infusion seven to anticipatory distress at infusion eight we conducted one additional regression analysis. Using a hierarchical approach, we entered all other predictors (i.e., trait anxiety, distress before the first infusion, and posttreatment side effects) before examining the unique contribution of posttreatment distress to anticipatory distress. Results indicated that posttreatment distress accounted for additional significant variability in anticipatory distress even after accounting for the variability attributed to all the other predictors ($p < .01$).

Relation between Anticipatory Distress and Anticipatory Nausea: It is conceivable that anticipatory distress could, at least in part, be secondary to anticipatory nausea. However, in this study the incidence of anticipatory distress (> 90% at every infusion) was considerably higher than that of anticipatory nausea, which ranged from 6% to 36% across infusions. Thus, the vast majority of women reporting distress did not report concurrent anticipatory nausea. Moreover, including anticipatory nausea intensity at infusion 8 as a predictor in the stepwise regression described above did not alter the results. Posttreatment distress remained the strongest predictor, while anticipatory nausea intensity was not significantly related ($p = .50$) to anticipatory distress.

7. CONCLUSIONS

In this study, we sought to examine the relative importance of several predictors of anticipatory distress in women receiving chemotherapy for breast cancer. The results of this study indicate that the predictors of anticipatory distress vary over the course of repeated infusions of chemotherapy, with classical conditioning factors being most strongly related at later infusions. In the discussion that follows, we summarize the results and consider each in relation to the literature. We then consider the clinical implications of these results and discuss the potential utility of clinical interventions to alleviate anticipatory emotional distress in patients receiving chemotherapy treatment.

The present study provides two new lines of evidence supporting the view that conditioning processes contribute to anticipatory distress in patients receiving chemotherapy for cancer. First, the relative importance of a conditioning variable as a predictor of patients' experiences of anticipatory distress was demonstrated. Consistent with its hypothesized role as an unconditioned response, we found that the intensity of patients' posttreatment distress became significantly related to

anticipatory distress by the fourth infusion and became the strongest predictor of anticipatory distress by the sixth. Second, a direct relation between posttreatment distress and anticipatory distress was established by use of a path analysis. Furthermore, a hierarchical regression analysis confirmed that after statistically controlling for the contribution of all other predictors, the relations between posttreatment distress and subsequent anticipatory distress remained significant.

Three additional sets of findings indicated that anticipatory distress may also have a nonconditioned component. First, patients' levels of trait anxiety were directly related to anticipatory distress before only the first infusion. The path analysis indicated, however, that trait anxiety may have an indirect effect on subsequent anticipatory distress through its influence on patients' apprehension about chemotherapy before they have any personal experience of it (operationally defined as distress before infusion one). Second, patients' apprehension about chemotherapy significantly contributed to the intensity of their anticipatory distress at every infusion. The direct influence of patients' apprehension was confirmed by the path analysis. Third, the number of posttreatment side effects predicted patients' anticipatory distress levels at infusions three and five. Patients who experienced more posttreatment side effects were more likely to experience anticipatory distress at these infusions. This relation may reflect patients' cognitive expectations of aversive side effects based on past experience. However, it is not yet clear why this relation may be stronger at some infusions than at others.

The results of the present study support and extend three previous reports (5,9,15), which are consistent with the view that classical conditioning processes contribute to patients' levels of anticipatory distress before chemotherapy infusions. Extending the findings of these studies, the present study is the first to demonstrate the relative importance of posttreatment distress (putative unconditioned response) as a predictor of anticipatory distress. Indeed, we found that the intensity of posttreatment distress was the strongest predictor of anticipatory distress at infusions later in the course of treatment. Moreover, the path analysis indicated that the intensity of patients' posttreatment distress was directly related to their anticipatory distress prior to the eighth infusion, and the hierarchical regression further confirmed that this relation was independent of the other predictors. One must, however, be cognizant of the potential for unexamined confounding variables inherent in clinical studies such as these. In the absence of experimental verification, one cannot accept the conditioning hypothesis without reservation.

Further support for the conditioning hypothesis comes from a recent study that employed an experimental model of conditioned distress in chemotherapy patients (20). In this experimental study, patients were randomly assigned to either have presentation of a distinctive beverage systematically paired with chemotherapy

administration or not. After several such pairings, the beverage was presented to patients in their homes (in the absence of clinic cues or impending chemotherapy). Patients in the experimental group (who had previously had the beverage paired with chemotherapy infusions) had increased levels of distress after the beverage presentation. Control patients (who had never received the beverage in conjunction with treatment) did not. This experimental study provides compelling evidence that patients can develop a conditioned distress response to a cue explicitly paired with chemotherapy. Complementing these results, the present study suggests that anticipatory distress before chemotherapy infusions represents a conditioned response to ordinary clinic cues.

Consistent with the literature on anticipatory nausea (21,22), the present study suggests that multiple conditioning trials (i.e., chemotherapy infusions) may be necessary before the conditioned component of anticipatory distress is detectable. The need for multiple conditioning trials in the development of conditioned anticipatory distress is consistent with neo-conditioning theory (23), which postulates that the strength of an acquired fear reaction is determined by the number of times there is an association between the conditioned stimulus and the unconditioned response.

In the present study, as in a previous study (9), trait anxiety was found to be related to the intensity of patients' distress before the first infusion of chemotherapy. Interestingly, we found that following experience with chemotherapy treatment, patients' levels of trait anxiety were no longer predictive of their subsequent anticipatory distress. Indeed, the path analysis at infusion eight confirmed that trait anxiety was not directly related to the intensity of anticipatory distress, although it was indirectly related through its influence on patients' apprehension about chemotherapy. These results are consistent with the view that the effects of trait anxiety may be more pronounced with novel stressors (24).

Consistent with our prior research (9), patients who had higher levels of distress before their first infusion of chemotherapy reported greater anticipatory distress before all subsequent infusions. Although distress before the first infusion is clearly a powerful predictor of subsequent anticipatory distress, the sources of such apprehension about chemotherapy remain to be determined. In addition to trait anxiety, a myriad of psychosocial and treatment-related factors could play a role. For example, it is likely that patients have expectations about the aversiveness of chemotherapy based on reports from family, friends, the media, and/or medical personnel. Additionally, patients' apprehension may be based on prior unpleasant experiences with medical procedures, such as biopsy and surgery. Alternatively, distress before patients' first infusion of chemotherapy may be, in part, a conditioned response. Analogous to "white coat hypertension" (25), patients may have formed conditioned distress responses to medical clinics due to previous anxiety-provoking

interactions. Finally, one must also consider possible external sources of distress, including hassles associated with treatment visits (e.g., traveling to the clinic, arranging for child care, taking time off from work). These potential sources of distress should be examined in future research.

Contrary to our previous research (9), the number of side effects patients experienced after an infusion was not related to the subsequent intensity of anticipatory distress at all infusions.

The apparently less robust finding in this study could reflect differences in the statistical analyses performed. The previous study forced this variable into hierarchical regression analyses prior to the posttreatment distress variable (putative unconditioned response), such that any shared variance of side effects with posttreatment distress would be attributed only to the number of side effects experienced. In the present study, we examined the relative influence of each variable in stepwise regressions, which enter the variable that accounts for the most variance on the first step; shared variance with other predictors would thus be attributed to that variable ("winner takes all" approach). It should be noted that in both studies, the influence of side effects may have been underestimated because of the methodological constraints of the measure. Simply counting the number of side effects results in a variable with a limited range, which reduces the likelihood of finding significant effects. It is possible that patients' ratings of the intensity of side effects would be a better predictor of their levels of anticipatory distress. Although we assumed that patients' negative expectations of side effects are the result of their previous experience of side effects, the nature of this relation was not established in the present study. Perhaps assessments of patients' actual expectations would be more predictive of anticipatory distress. However, contrary to this possibility, a previous study (9) has shown that patients' expectations of side effects (at least when assessed prior to the start of treatment) are not related to subsequent anticipatory distress. Future researchers should thus consider directly assessing patients' expectations of side effects prior to each chemotherapy infusion.

It is important to note that the present study did not examine a multitude of psychosocial factors that could modify patients' levels of distress. For example, patients who respond to their cancer diagnoses and treatments by employing certain coping processes (e.g., escape-avoidance) have been found to have more emotional distress (26-28). Another psychosocial factor that might influence distress levels is social support. Research has demonstrated that women with a chronic medical condition have higher levels of distress when they receive negative support from their husbands (29). It seems unlikely that the inclusion of these psychosocial factors would have affected the significant relation between posttreatment distress and anticipatory distress in the present study. However, in future examinations of these

factors, investigators may wish to consider their influence within a conditioning framework.

More than 90% of patients in the present sample reported distress before each infusion. Results from the present study indicate the importance of conditioning to this anticipatory distress and suggest ways in which interventions based on conditioning principles could be therapeutic. For example, reducing posttreatment distress (putative unconditioned response) should reduce subsequent (conditioned) anticipatory distress. Reduction of posttreatment distress could be accomplished in at least two ways. First, pharmacologic agents (e.g., anxiolytics) taken after chemotherapy infusions might be used to substantially reduce posttreatment distress. Behavioral interventions, such as relaxation training, could also be implemented to decrease emotional distress. Support for this possibility can be found in the literature on anticipatory nausea and vomiting in cancer patients. Chemotherapy patients trained to use relaxation techniques to control nausea experienced less posttreatment nausea and were also less likely to develop anticipatory nausea (30,31). Further research is needed to assess the efficacy of such interventions in reducing or preventing conditioned emotional distress in chemotherapy patients.

9. TECHNICAL ISSUES

Since the time that the grant was submitted there has been a change in standard clinical care in the Breast Service at Memorial Sloan-Kettering Cancer Center, such that patients recruited for the research study are no longer routinely being monitored (at the patient's expense) for neutropenia between treatment infusions. This change has made it more difficult to achieve compliance with the proposed twice-weekly CBC with differential for the research protocol and has increased the cost per subject for the research project.

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Chapter 10

PSYCHOLOGICAL STRESS AND UPPER RESPIRATORY ILLNESS

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INTRODUCTION

Accumulating evidence from both naturalistic and experimental studies indicates that psychological stress can affect upper respiratory illness (URI). This literature has recently been reviewed in considerable detail by three separate research groups with complementary perspectives.[1-4] In their reviews, Boyce and Jemerin focused on infectious illness in children, emphasizing the role of individual differences in susceptibility.[1,2] Cohen and Williamson reviewed the broader literature on stress and disease in humans, with an emphasis on psychological factors.[3] Peterson and colleagues, on the other hand, reviewed both human and animal studies, with an emphasis on biological factors.[4]

Our purpose in this chapter is not to present another exhaustive review of the literature on psychological stress and URI, but rather to highlight some of the important issues for this area of research, as well as research conducted since those previous reviews. Throughout the chapter, our focus will be on human URI. We will usually focus our consideration of URI to the common cold, both because colds are the most common URI, and because colds have been the most frequent subject of studies on psychological stress in URI.

This chapter is divided into five sections. The first section provides a brief introduction to the various ways stress has been conceptualized in psychobiological and health studies. The second section provides an overview of upper respiratory disease, including etiology, pathophysiology, and immune defenses. The third section outlines the steps in the pathogenesis of URI where psychological stress could conceivably exert its influence, and possible mechanisms of such stress effects are discussed. The fourth section provides illustrative examples, organized by study design (cross-sectional, longitudinal, and viral exposure), of studies that have examined the association between stress and URIs. The fifth section provides a summary and recommendations for future research.

WHAT IS PSYCHOLOGICAL STRESS?

There has been considerable debate concerning the definition of psychological stress.

At least four different ways of conceptualizing stress have been discussed.[5-7] 1) The *environmental approach* defines stress as significant, objective changes in the environment. Some environmental definitions are based solely on the degree to which events require readjustment in one's lifestyle, whereas other definitions are based on the extent to which events are upsetting. Examples of this approach are the studies of major life events (e.g., death of spouse, change in employment, major purchase) and daily minor events (e.g., argument with spouse, problem at work, issues with children). 2) The *appraisal/emotion approach* defines stress as judgements of a situation as challenging or threatening (appraisal approach) or as the experience of negative emotions, such as anxiety or sadness (the emotion approach). This conceptualization hinges on psychological reactions to environmental events. 3) The *physiological approach* defines stress in terms of relatively stereotypic alterations in physiological processes. Examples of stress defined this way include activation of the hypothalamic-pituitary-adrenal axis (e.g., evident in increased plasma cortisol concentrations), or activation of the autonomic nervous system (e.g., evident in increased blood pressure). 4) The *integrative approach* defines stress as certain combinations of the above elements. An example of this approach is Lazarus' transactional model of stress and coping.[8] According to this model, stress is the result of a unique interaction of environmental change, specific appraisals, and coping efforts to modify emotions and/or problems. It is conceptualized as a temporally changing process (hence, transactional), which includes feedback from later processes that can, in turn, affect earlier processes.

A common characteristic of these conceptualizations of stress is that an external stimulus of some sort (a stressor) is always thought to be involved. It is also commonly presumed that stress has the potential to result in a negative health outcome.[7] In the review that follows, we have included studies that examined relations between URI and either some external stimulus (stressor) or some change in appraisal or affect. For the purpose of this review, defining stress as a physiological response seems, to us, conceptually too closely related to URI. We have limited our review to studies of clear environmental changes that are perceived as unpleasant or stressful. We have not included articles of more general psychological states (e.g., personality) which may have their own effects on URI.

UPPER RESPIRATORY INFECTION

Background

Nationwide annual surveys regularly indicate that URI is the single most common cause of physician visits and missed days of work among all acute medical conditions.[9] In 1990, Couch[9] estimated that the common cold and influenza accounted for 165 million significant illnesses, resulting in an average of 3.2 days of restricted activity and 1.6 days in bed; half of those illnesses received medical attention. It has been estimated that upper respiratory symptoms precipitate as many as 14% of all visits to physicians.[10] The common cold has been calculated to be responsible for 30 million lost days at school and work each year; to cost $3 billion for physician office visits; and to cost $2 billion for over-the-counter drugs.[11] Common colds, although not serious medical conditions, thus pose a major public health problem.[10]

The incidence of common colds is highest in infants and children, who suffer from four to eight colds each year; adults typically get two to five colds, except in households with children, where the incidence is higher.[12] Indeed, children's noses have been characterized as

the chief reservoir for cold viruses,[10] with dissemination into the broader community occurring as infection moves from school to home, where parents become infected.

The viruses responsible for colds (see below) are transmitted by airborne droplets and aerosol (e.g., by sneezing), as well as through environmental contamination with virus-laden nasal secretions (e.g., by touching the eyes or nose with contaminated fingers).[12] For example, rhinovirus in nasal secretions of an infected individual has been demonstrated to be easily spread by the fingers to a variety of common household objects (e.g., doorknobs), where it can survive for several hours, serving as a source of infection.[13]

INFECTIOUS AGENTS

Rhinoviruses are the most common cause of the common cold.[13] Based on survey studies with samples collected for viral identification, rhinoviruses have been estimated to be responsible for 40 to 60% of all colds in adults.[9] The virus can either be identified in nasal secretions from the infected individual or by the presence of specific antiviral antibodies in serum or nasal secretions following infection.[13] More than a hundred different types of rhinoviruses (serotypes) have now been identified.[13] Coronaviruses (3 types), which are technically more difficult to identify, have been estimated to be responsible for another 20% of colds in adults and perhaps more in children.[9] Other viruses known to be associated with classic cold symptoms (e.g., rhinorrhea) include the influenza viruses (3 types), parainfluenza viruses (4 types), and respiratory syncytial virus; if not contained by host defense mechanisms, these viruses typically go on to cause more serious illness and associated systemic symptoms (e.g., fever).[9]

SYMPTOMS OF INFECTION

The multitude of different upper respiratory viruses, reviewed above, all typically cause a strikingly consistent constellation of symptoms including rhinorrhea, nasal obstruction, sneezing, pharyngeal discomfort, and cough, which are familiar to all of us as a common cold.[9,10,13,14] It should be noted, however, that for reasons that are as yet obscure, about a third of all verified rhinovirus infections have been found not to result in symptomatic illness (i.e., in clinical colds).[13] For many adults symptoms begin with a dry, "scratchy," or sore throat, soon followed by a watery nasal discharge, inflammation of the nasal mucosa, and sneezing.[12] Some systemic symptoms such as general malaise and myalgia may be evident, but fever is rare.[12] After one to three days, nasal obstruction is common, the nasal secretions thicken and are no longer clear.[12] In infants, fever and other systemic symptoms including anorexia, vomiting, and diarrhea are more commonly associated with colds.[12] Symptoms typically begin to decline within a few days and last for about a week, although in some cases they may linger for as long as a month.[15]

Confirming the commonality of symptoms across different infectious agents, a recent study conducted at the Common Cold Unit in England conducted detailed symptom assessments of viral shedding following exposure of healthy subjects to several different URI viruses.[16] Three different rhinoviruses, a respiratory syncytial virus, and a coronavirus were administered to quarantined volunteers, and symptoms were carefully monitored over the next several days. Although there were some modest differences in the rapidity with which symptoms developed, suggesting differences in the incubation period, by two to three days after

the viral exposure, symptoms peaked. There were no major differences in the pattern of symptom development across the five viruses.

The ubiquity of this symptom constellation across different viruses suggests common pathogenic mechanisms (see below) and raises the possibility that these symptoms may confer an adaptive advantage to the infected individual. Ewald[17] has theorized that from an evolutionary perspective, symptoms of infection can be viewed as either: 1) adaptations of the pathogen to increase its reproductive success; 2) adaptations of the host to defend against the pathogen; 3) "side effects" of the infection that do not serve adaptive functions for pathogen or host. Which role is played by the symptoms of a common cold has yet to be determined.

ASSESSMENT OF ILLNESS

As might be expected from the discussion above, the literature includes two ways of assessing URIs: the presence of the symptom syndrome (clinical cold) or the presence of an infection, verified by isolation of virus from nasal secretions or by increases in specific antibody titers. As will be discussed below in the section on viral exposure studies, individuals can manifest an infection yet not demonstrate the clinical syndrome. Although one might demand that both infection and syndrome be present as a conservative definition of URI, this would virtually eliminate the study of URI in natural observation studies. The reason for this is that it is difficult to confirm viral infection when the particular virus is not known, which is the typical case in epidemiological studies of URI syndromes. Viral exposure studies can, on the other hand examine both clinical syndromes and infection (because the strain of virus is known and can be specifically tested for).

IMMUNE DEFENSES AND THE PATHOGENESIS OF RHINOVIRUS INFECTION

Neither the pathogenesis of infection nor the relevant immune defenses is well understood for any of the more than 200 distinct viruses known to infect the human upper respiratory tract.[9] In the discussion that follows we will again focus on the rhinoviruses, the pathogenesis of which has been under increasing scrutiny in a series of experimental inoculation studies.[12]

Besides avoiding exposure to the rhinovirus, the best established initial immune defense against infection is the presence of protective levels of specific antibody for the virus as a result of previous exposure.[13] An early study by Hendley and colleagues[18] revealed an inverse relation between individuals' levels of serum neutralizing antibodies to the challenge rhinovirus and their subsequent susceptibility to experimental infection. More recent research, using a more sensitive ELISA assay, has continued to indicate the protective value of specific antibody to the challenge virus in either serum or nasal secretions prior to experimental inoculation.[19] Immunoglobulin in nasal secretions, predominantly secretory Immunoglobulin A (sIgA), but also including Immunoglobulin G (IgG), is thought to reduce the risk of infection by interfering with viral attachment to the epithelial surface.[20] It should be noted that the nasal mucosa has a wide range of nonspecific defense mechanisms that are also likely to play a preventative role; not the least of these is the outer layer of the mucous blanket itself, which by ciliary action transports particles to the posterior pharynx where they are swallowed.[21]

Although the protective role of secretory antibody at the mucosal surface is widely accepted, the relative importance of secretory and circulating antibody is still debated, with some investigators arguing that circulating antibody may be responsible for long lasting immunity.[22] It is also too early to rule out possible contributions of cellular defenses, whose role at mucosal surfaces has received little attention.[23]

Viral infection is, beyond a doubt, the critical initiating step in the pathogenesis of a clinical cold, but the chain of events leading from infection to the manifestation of symptoms has yet to be fully elucidated.[24] Several lines of evidence suggest that the virus itself is not directly responsible for symptoms. First, it is quite possible to be infected and have no symptoms. Typically, in both experimental studies and field studies, a third of the subjects with confirmed infections have no symptoms.[13] Second, histological studies with light and/or electron microscopy have found that rhinovirus infection, unlike influenza, does not cause damage to the nasal epithelium.[25] Third, although symptoms tend to be most severe when viral shedding is at its peak (e.g., day 2), shedding typically continues for several days after symptoms have resolved.[25] Fourth, accumulating evidence indicates that viral infection triggers the release of inflammatory mediators, which in turn cause the symptoms.[13]

Increased levels of kinins (e.g., bradykinin and lysylbradykin) have been found in the nasal secretions of symptomatic but not asymptomatic individuals, following both natural and experimental infection with rhinovirus.[26,27] Consistent with the possibility that kinins may play a role in symptomatology, provocation experiments have shown that nasal application of bradykinin causes rhinorrhea, nasal obstruction, and sore throat in volunteers.[28] In addition to their direct effects on vascular permeability, a major contributor to nasal secretions early in the course of a rhinovirus infection,[29] kinins are thought to affect local secretory responses and pain by stimulating nerve fibers in the nasal mucosa.[28,30] Although neural regulation of nasal secretions is complex and, as yet, poorly understood, both cholinergic and sympathetic nerves are thought to regulate the passive diffusion of plasma proteins, as well as active secretions (including sIgA) from serous and mucous glands.[21,31] Psychological influences could thus affect the secretion of kinins or the neural regulation of nasal secretions.

Unlike allergic rhinitis, no increases in histamine or prostaglandin D2 have been found in nasal secretions following rhinovirus infection, suggesting that mast cells may not play a role in the symptoms of a cold.[26,27] The severity of symptoms has been found to be correlated with an increase in the numbers of lymphocytes and neutrophils in nasal secretions.[25,32] Increased numbers of neutrophils have also been histologically documented in biopsies of the nasal mucosa of symptomatic individuals.[25] One possible explanation for these effects is suggested by a recent study indicating that nasal lavage fluids from symptomatic subjects contained significantly higher levels of interleukin-1 (IL-1) than asymptomatic, or sham-infected, subjects.[24] It is tempting to speculate that this IL-1 reflects the activation of local cellular defense mechanisms, but IL-1 is known to be secreted by a wide variety of nonlymphoid tissues, including nasal epithelial cells.[33,34] In any case, local secretion of IL-1 could upregulate a wide range of both local and systemic cell-mediated immune defenses.[33]

The mechanisms responsible for recovery from rhinovirus infection are not yet clear. A role for local and/or systemic neutralizing antibody cannot be ruled out, although in most studies increased levels of specific antibody have not been detected until the illness has resolved.[13,15] As with other viral infections, cellular immune defenses may play an important

role in recovery, although local secretion of interferon may also be involved.[13] Although direct evidence for cell-mediated recovery mechanisms is lacking, there is some circumstantial support. As noted above, the number of lymphocytes and neutrophils in nasal lavages from infected subjects is significantly elevated within the first few days after experimental infection with RV25, raising the possibility that leukocytes in the nasal mucosa may play a role in resolving the infection.[32]

There is also some initial evidence consistent with the possibility that systemic cellular responses may play a role in resolving the infection. For example, three days after infection with the same rhinovirus serotype (RV25), Levandowski and colleagues[32] found decreases in peripheral blood lymphocyte numbers (including T cells, but not B cells); the decreases in cell numbers were inversely correlated with the number of days of viral shedding. Three days after infection with a different rhinovirus (Hanks), Hsia and colleagues[35,36] found no change in lymphocyte numbers, perhaps reflecting differences in the kinetics of infection which have been demonstrated across different viruses.[14,16] After five days, however, these investigators[36] found significant increases in lymphocyte numbers (including T cells, but not B cells). *In vitro* assessment of isolated peripheral blood mononuclear cells (PBMC) revealed increased levels of PHA-stimulated interleukin-2 and interferon production, which were inversely correlated with the duration of viral shedding. Confirming a previous report,[37] these investigators also found that the *in vitro* proliferative responses to the challenge virus were also increased following infection, as was natural killer (NK) cell activity.[36] *In vitro* proliferative responses to the challenge virus were also found to be increased following experimental infection (RV39) in another recent study,[38] but these investigators found reduced levels of NK cell activity in peripheral blood mononuclear cells collected seven days after infection.

All of these studies can be viewed as consistent with the possibility that cell mediated responses may play a role in recovery from rhinovirus infection, but none provides proof. The immune mechanisms responsible for recovery from rhinovirus infection remain to be determined. Although it is tempting to theorize that mucosal immune defenses must be more critical in resolving what is widely accepted as a localized infection,[13] systemic responses to rhinovirus may also play an important role. Indeed, there may be a false dichotomy in this thinking. Optimal recovery will likely depend on local and systemic responses working in concert.

HOW COULD PSYCHOLOGICAL STRESS AFFECT URIs?

There are several points in the pathway of pathogenesis where stress could affect URI, as is schematically shown in Figure 1. First, psychological stress may alter exposure to virus in some way. For example, people experiencing high stress levels may cope with the stress in ways that encourage exposure (Arrow #1). One method of coping with stress is called seeking social supports,[39] and it involves procuring practical advice and/or emotional support from others. This contact with others, some of whom may be shedding URI virus, could increase exposure to pathogens.

Lowered host prevention mechanisms to initial viral exposure is a strong possibility for mediating stress effects (Arrow #2). There is substantial research showing that psychological stress affects immune system function,[40] including many of the immune components previously discussed (e.g., sIgA). Stress may alter immunity by affecting behaviors such as sleep patterns,

eating, consumption of alcohol medication use, and exercise.[41] It has also been shown that stress can affect immunity via direct neural connections and/or hormonal changes (reviewed in previous chapters).

Similar to host prevention mechanisms, the immune system is thought to play a role in controlling viral replication in the nasal mucosa (Arrow #3). Both cellular and humoral systems probably contribute to controlling viral replication and both are likely to be influenced by the same stress-related factors mentioned for host prevention mechanisms.

Fig 1. Possible ways that psychological stress could affect URIs

Clinical syndrome refers to the constellation of symptoms associated with URIs (mentioned above). It is important to note that URI does not always lead to clinical syndromes; as noted earlier, for rhinovirus only about two thirds of those infected (confirmed by viral shedding and/or raised antibody titers later) manifest symptoms. There is currently no explanation for this discrepancy, but clearly there must be individual differences in the physiological processes that affect symptom expression. Psychological stress may contribute to the individual differences by affecting the underlying processes responsible.

Recovery from a clinical syndrome usually takes several days. Stress could potentially influence the processes that are responsible for determining the duration of infection and symptoms (Arrow #5). In addition to physiological processes, stress could influence patients' use of medications.

Finally, after the experience with URI viruses, the immune system will be better poised to defend against future infection through both specific (e.g., secretory antibody response) and nonspecific mechanisms. Psychological stress has been shown, for example, to affect antibody response to vaccination.[42] It may be that psychological stress influences the magnitude of this secondary response.

Although there may be other routes by which psychological stress influences URI, these six routes are likely candidates. As will be evident from the discussion below, many of these routes have not yet received any research attention.

REPRESENTATIVE STUDIES EXAMINING THE ASSOCIATION BETWEEN STRESS AND URIs

Cross-sectional Field Studies

A number of studies have been conducted exploring associations between naturally occurring stressors and URI symptomatology. Some of these studies examined objective indices of URI infections as well. These studies provide support for the hypothesis that stress is associated with URI, yet clearly much research remains to be done.

Graham *et al.*[43] reported a survey of 2,618 children and their families in Australia. The survey examined the association between the mothers' stress and URI symptoms in children. Families were selected for the study if the proband (the child) fell into either the upper or lower quintile of the distribution of URI symptoms over the last year. Mothers' stress was assessed by a combination of scores on a major life event checklist, a daily hassles checklist, and an emotional distress scale. Mothers were labelled as stressed if their scores on all three measures were above the median. These procedures yielded a sample of 255 children with frequent URIs and 227 with infrequent URIs. Their average age was about 2.5 years. Children whose mothers were in the high stress group were four times as likely to be in the high URI group than those whose mothers were in the low stress group. Although other risk factors significantly contributed to a model developed by the investigators to predict URI group membership (e.g., chest illness in the child's first year of life was a strong predictor), the mothers' stress level was the second most powerful predictor of URIs. The investigators acknowledge the bidirectional interpretations that are consistent with this data, namely, that mothers of ill children may be stressed for that reason or that their stress causes increased illnesses. Regarding the latter hypothesis, it may be that a decrement in family hygiene due to the mother's stress or enhanced susceptibility of children could be operative.

A negative finding was shown in a study notable for its verification of infection. Clover *et al.*[44] studied 281 adults and children during an influenza outbreak. Sixty six subjects developed verified influenza: 35% of the children and 17% of the adults. A major life events inventory was administered yet showed no association with influenza status. However, a measure of family cohesion was negatively related to infection.

LONGITUDINAL FIELD STUDIES

Longitudinal studies have followed subjects on more than a single occasion. They have many of the same methodological weaknesses as cross-sectional field studies. The studies are correlational and, hence, cannot rule out third variable explanations for observed relations. However, the repeated measurements of both stress and URI allow for predictions of URIs from levels of stress reported *before* URIs are reported. Such prospective prediction allows stronger statements about causal relationships between stress and URI. Despite this strength, data from longitudinal studies have often not been analyzed in ways that capitalize on prospective prediction.

An excellent example of an early longitudinal field study is one that was conducted by Roghmann and Haggerty.[45] In this 1973 study, 512 families were monitored over a 28-day period by mothers. Using a health diary, mothers recorded significant events that were perceived as stressful (e.g., losses, arguments, financial problems), as well as health symptoms in each family member and his or her medical care utilization. Unlike many survey studies, these investigators utilized the longitudinal data in sophisticated ways, which served as a model for later studies of stress and health. Although the authors did not specifically analyze URIs, they state that most illnesses included fevers, coughs, headaches, and "colds." It is thus very likely that the vast majority of the illnesses analyzed in this study were URIs.

Considering all of the members of families studied, a total of 71,346 person-days were examined. On a day-by-day basis, the investigators found that 30% of the days could be characterized as stressful, but only 10% were found to be in the upper range of the stress score. A health complaint was reported by mothers about themselves on 25% of days, and for their youngest child on 17%. Same-day analyses showed that the probability of a mother having an illness doubled when stress was present on that day versus when it was not present; a 50% increase was observed for the youngest child. However, the most powerful analyses were based on the notion of stress and illness *episodes*. In accord with the commonsense notion that difficult times tend to stretch over multiple days and that the same is true for illnesses, the authors analyzed the correspondence between episodes of stress and illness. Importantly, they analyzed the data such that lagged associations would be evident: that is, stress episodes preceding illness episodes and vice versa. They found a 250% increase in illness episodes following stress episode onsets compared to what would be expected by chance, suggesting a causal relation.

In another of the earlier studies of URI in children, Boyce *et al.*[46] repeatedly assessed 58 children in a daycare setting. Children (average age 4 years) were observed on a daily basis on weekdays for an entire year, during which time all illnesses were assessed by a nurse practitioner. Additionally, biweekly nasopharyngeal cultures were taken; cultures were also taken at the start of each illness. At the end of the year, parents completed several questionnaires, including a major life events inventory for events in the child's life and a

questionnaire about weekly family routines. Observational data yielded several measures of illness: frequency, average duration, average severity, and a composite measure (days of illness times average severity). When age, sex, race, family income, and family size were controlled, results indicated that the child's life event stress was associated with illness duration. More life stress was associated with longer illnesses. Interestingly, life event stress interacted with family routine such that those children with high stress and strong family routines had more severe illnesses than other children. It is important to note that stress was not associated with frequency of illness. In contrast to the previous study, these results are less convincing since prospective analyses (lagged relations) were not computed.

In the 1980s a number of studies examined the associations between minor symptomatology and two types of stress: major life events and daily events/hassles. At issue was not the nature of the association between stress and illness, but the then recent emergence of minor event and hassle checklists as a way of assessing stress. Therefore, the goal of these studies was to compare how well minor versus major events could predict symptomatology. Since the focus was not on the symptoms, it is often not clear exactly what sorts of symptoms respondents reported. Importantly, the concept of symptom episodes was not part of the methodology, making it difficult to know what a total symptom score meant (several individual days of symptoms or a few long episodes, etc.). Despite these shortcomings, several of these studies demonstrated that major life events and minor events both predicted symptom rates, with the edge going to minor events.[47,48]

Stone, Reed, and Neale[49] conducted a study capitalizing on the prospective associations of daily data collected in a longitudinal manner. Seventy nine community-dwelling, middle-aged, married males were studied for 84 consecutive days. An important feature of this study was the careful assessment of daily events. Husbands completed the daily event questionnaire about themselves each evening and their wives confirmed the reports of husbands' events (prior work had shown that this procedure improves event reporting). Another important design feature of this study was that questionnaires were completed on a daily basis and mailed to the investigators on the following day; this procedure has been shown to reduce the possibility that subjects complete multiple days at one sitting.[50]

This study following the conceptualization of URIs used by Roghmann and Haggerty,[45] isolating episodes of symptoms with symptom clusters consistent with a cold or flu (unlike Roghmann and Haggerty, however, no single-day episodes were allowed). The frequency of desirable and undesirable daily events was examined for several days prior to the onset of URI episodes. For control periods, days that did not precede URIs (matched for day of the week as well) were selected from the same subject. An increase in undesirable events and a decrease in desirable events were observed in the three to five day period prior to URIs relative to control days. Notably, there were no differences in event report, either desirable or undesirable, one or two days before URI onsets. This pattern of data makes it less likely that there was a reporting of subsyndromal symptoms, not recognized by subjects, since the most likely period for such an effect to be observed would be immediately before the URI onset.

Three additional studies have extended the Stone, Reed, and Neale[49] findings. Evans, Pitts, and Smith[51] replicated the dip in desirable events preceding URIs, using a similar methodology to that of Stone *et al.*[49] However, these investigators did not observe an increase in undesirable events prior to the onset of URIs. In an independent study, Evans and

Edgerton[52] again found a decrease in the frequency of desirable events before URIs, and this time they observed a trend for an increase in undesirable event frequency. Finally, Stone, Porter, and Neale[53] examined the same association in yet another longitudinal, daily diary study. No replication of either a dip in desirable events or a peak in undesirable events was observed. A comparison of the methods and analytic techniques employed in all four of these studies can be found in Stone, Porter, and Neale,[53] but suffice it to say that the bulk of the evidence is in favor of an effect of fewer desirable events and, less strongly, more undesirable events prior to URIs.

VIRAL EXPOSURE STUDIES

Naturalistic studies have the advantage of ecological validity[54] because subjects are exposed to "real" levels of stressors and naturally occurring exposures to pathogens. A disadvantage of these designs is that determining causal pathways is difficult because stressor and pathogen exposures are not controlled. Viral exposure studies can address these problems. These studies typically manipulate exposure to selected pathogens and can manipulate stressor levels as well, unlike field studies where the pathogen responsible for the URI symptoms is usually not identified (in part, because any of scores of viruses could be responsible). We should note, however, that given the expense of these types of studies, only a handful have been conducted, and these examined a very small selection of URI viruses.

One of the first studies exploring stress and experimentally-induced URI came from the Common Cold Unit (CCU) in England.[55] The CCU conducted a series of studies designed to understand the pathophysiology of the common cold by inoculating healthy individuals with live cold viruses. In 1977, Totman *et al.*[55] explored whether cognitive dissonance produced by a difficult decision paradigm was related to the incidence of infection or to cold symptoms in individuals exposed to either of two rhinoviruses. Although stress was not explicitly assessed, subjects who experienced decision making may be thought of as being stressed by the procedure (an interpretation advanced by the authors). After controlling for pre-existing antibody levels to the challenge viruses, "stressed" subjects had significantly higher levels of symptoms, but no differences in the incidence of infection or the amount of shed virus in nasal secretions.

A second study by Totman[56] from the CCU paradigm explicitly examined life event stress. In addition to the life event checklist, an interview fashioned after Brown's method[57] of objectively recording major experiences was used to create several stress indices. These included the SEI, assessing the time-adjusted impact of events, the SDI, assessing the total magnitude of life events, the TLI, assessing changes in "goal-directed" activities due to events, and the TCI, another measure of change in activities due to events. Measures of extroversion and neuroticism were also administered. After controlling for preantibody status prior to the experimental inoculation with the viruses, only the TLI was associated with total symptom score. Only the TCI was associated with amount of viral shedding. These relationships were complicated by the overlap between the stress measures associated with response to viral exposure (TLI and TCI) and extroversion, which had the strongest association with both symptoms and viral shedding. Regression analyses controlling for the overlap did, however, show that the TCI had an independent effect on shedding over that explained by extroversion.

More recently a landmark study by Cohen *et al.*[58] also at the CCU showed that levels of stress prior to inoculation with live virus were associated with susceptibility to and clinical syndromes of several URI viruses. In this study, 394 volunteers were exposed to one of several URI-inducing viruses. A psychological stress index was created by combining three separate stress scales that were administered upon entry to the CCU: a life events inventory, the Perceived Stress Scale, and a negative affect scale (for the past week). After controlling for pre-existing antibody levels to the viruses and for a variety of subject variables (e.g., age, sex, education, allergic status, weight, season), the association between the stress index and two outcomes was examined. Outcomes were: 1) the percentage of subjects who became infected with the experimental virus, as indicated by isolation of the shed virus or by increase in antibodies to the virus, and 2) the percentage of subjects who manifested clinical cold syndromes. For infection, there was a linear rise in proportion of subjects infected as stress levels increased. At the lowest stress levels, less than 75% of the subjects were infected, whereas at the highest stress levels, about 90% were infected. A parallel pattern emerged for the proportion of subjects with colds: at the lowest stress levels, under 30% had colds, while at the highest levels, about 45% had colds. This data provides some of the strongest evidence in support of the hypothesis that psychological stress affects URI.

A further analysis of the data from the Cohen, Tyrrell, and Smith[58] study explored relationships between individual components of the stress index and susceptibility to URI.[59] Analyses in this paper indicated a somewhat surprising set of associations. Only the life event measure was a significant predictor of clinical colds. In contrast, negative effect and perceived stress were significant predictors of infection.

A study by Stone and colleagues[60] essentially replicated the life event findings of the Cohen study in a smaller sample. Seventeen college undergraduates, all of whom had no pre-existing antibody titers to the experimental virus, were experimentally inoculated with a rhinovirus. At the outset of the study, subjects completed a life event inventory, resulting in a stress score reflecting the total number of events experienced in the last year, and a mood assessment. Because prior to entry into the study subjects were screened for having no antibody to the experimental virus, all subjects became infected after viral exposure (unlike the Cohen study where some individuals did have pre-existing antibodies to the experimental agents). Subjects were classified by whether or not they had a clinical cold: 12 of 17 (71%) did. Subjects who did not develop colds had fewer life events (2.6 vs. 7.3) than those who developed colds. Interestingly, when events were categorized according to subjects' perceptions, subjects without colds had fewer negative (nonsignificant) and more positive (significant) events. There were no differences in the groups of subjects in terms of negative or positive effect (an alternative way of conceptualizing stress).

PHYSIOLOGICAL MEDIATION OF PSYCHOLOGICAL STRESS AND URIs

With rare exception, the studies reviewed above have not directly examined possible mediating pathways that could be responsible for the associations between stress and URI. This comment should not be taken as criticism. It is appropriate that early investigators focus on establishing phenomenon before attempting to explain how it works. The validity of the demonstrated relations between psychological variables and URI is not compromised, after all,

by our current lack of knowledge concerning the mediating mechanisms. On the other hand, consideration of possible mechanisms might help to explain some of the apparent anomalies in the present literature and suggest improved strategies for detecting psychological influences in future research. For example, are there plausible mechanism(s) that could account for the apparent selectivity of the effects of life events on colds due to rhinovirus infection? As reviewed above, differences in life events were not found to predict which individuals would become infected following experimental inoculation with rhinovirus, but did predict who would develop the symptoms of a cold.[59,60]

As we discussed above, there are several possible pathways that could link psychological variables with URI. The problem is knowing where to begin. We present one line of research exploring a possible pathway that may mediate the effects of psychological stress on URIs.

Some of the strongest evidence reviewed above supporting the association between stress and URIs was from prospective daily diary studies. There have been two studies which have examined a potential immunological mediator of stress and URIs, secretory IgA antibody, which was mentioned in the section on pathogenesis of URI.[62] We focus here only on the studies using specific sIgA antibody to a known antigen and bypass studies that have examined stress and nonspecific sIgA protein, because it is not clear that total sIgA protein is a meaningful index of immunological protection. It is more likely that specific antibody to a known antigen behaves in an analogous manner to URI pathogens.

The immunologic model used in both studies[61,61] involved repeated challenge with a (relatively) novel protein for participants, purified rabbit albumin. Every morning for a number of consecutive days, subjects ingested 100 mg of albumin. Specific antibody responses were monitored via nightly saliva samples obtained directly from the parotid gland with a Curby cup. An index of antibody activity was obtained by dividing sIgA activity to the albumin (obtained through ELISA) by overall levels of sIgA protein (obtained through RID), in order to control for salivary flow rates.

The stressors differed in the two studies: in the first it was affective states (negative and positive moods) and in the second it was the number of undesirable daily events (and the number of desirable daily events as well). In both studies, effects of stress on sIgA antibody to the albumin were demonstrated. In the first study,[61] thirty dental students were studied over an 8 week period, 3 times per week. Days with high negative mood had lower levels of specific antibody activity compared to days with low negative mood. Opposite findings emerged for days with high and low positive mood; namely, high positive mood days were associated with higher levels of specific antibody. (Notably, these associations were not observed for total sIgA protein levels.)

The second study examined 96 community-dwelling, married males who participated for 12 consecutive weeks.[62] On a daily basis they recorded undesirable and desirable events as well as mood; an evening saliva sample (as described above) was also taken to examine sIgA response to the ingested antigen. On days with relatively high numbers of undesirable events, lower levels of sIgA antibody were observed. Conversely, days with higher numbers of desirable events were associated with higher levels of antibody. In addition to concurrent daily analyses, lagged analyses, where event levels on one predicted antibody on a latter day, were also computed. Surprisingly, the effect of undesirable events was limited to the same day, whereas the effect of desirable events appeared to last for two subsequent days. Additional analyses

explored the possibility that the effects of events on specific sIgA response were mediated through shifts in mood.[63] These analyses were consistent with the hypothesis: effects of both desirable and undesirable events were largely, although not exclusively, mediated through their effects on mood.

SUMMARY

This chapter has highlighted the substantial evidence from field studies and experimental viral exposure studies which suggest an association between psychological stress and URI. Overall, the majority of the studies found significant relations between stress and URI. The strength of the cross-sectional field studies is their epidemiological nature: large numbers of subjects were studied for an impressive number of days. Many of these studies focused on URIs in children, an important subject population given the high prevalence of URIs in this age group and their important role as a reservoir of infection. An additional strength of the prospective, longitudinal field studies is their attention to the timing of stress relative to URI. These studies generally show that stress precedes the onset of URI episodes. For example, several studies have found a significant increase in minor stressors a few days before the onset of URI symptoms. Of course, it is difficult to confirm infection in field studies. Exquisite control of viral exposure and intensive monitoring of symptoms (including objective measures such as mucosal weight) are strengths of the viral exposure studies. However, it must be noted that stress was not explicitly manipulated in these studies. The isolation of subjects that is required for these studies could be considered a stress-reducing intervention, as there may be fewer minor stressors compared to those experienced in the outside world. From the viewpoint of the psychological independent variable, these viral inoculation studies are not true experimental designs. As with the field studies, the relations between psychological stress and URI have been correlational. Nevertheless, the viral exposure studies represent the strongest evidence that stress can affect infection as well as symptoms of infection. It is particularly noteworthy that two independent studies have raised the possibility that the *symptoms* of URI may be affected by different types of psychological stress than the *incidence* of infection; these apparently selective effects can be best investigated in further viral inoculation studies.

We outlined several ways that psychological stress could affect URI, including influences on viral exposure, initial host susceptibility, viral replication, the clinical syndrome, recovery mechanisms, and the enduring protective immune response. Although there are many possible mechanisms by which stress could affect URIs, few have been examined. This focus is quite appropriate from the standpoint of public health issues. Regardless of the underlying biological mechanisms, significant effects of stress on the symptom syndrome in infected individuals could have a major impact on societal costs. Initial evidence indicates that stress may play a role in determining which infected individuals develop symptoms. Recall that nearly a third of those infected do not develop the clinical syndrome of a cold. These symptom-free individuals are unlikely to seek medical attention or to purchase medications. From a public health perspective, psychological effects on the incidence of infection are also important, of course. In addition to increasing the number of individuals with symptoms (who would then seek treatment), increased rates of infection due to stress could increase the pool of contagious

individuals, thus furthering the spread of the virus throughout the population.

Although one can cautiously conclude from the literature that there is an association between stress and URI, a number of issues remain to be investigated before we can fully understand the relations. Five of these were highlighted in the review by Cohen and Williamson.[3] (1) *Little is known about how the timing of the stressor and viral exposure influence the development of URI.* Some evidence suggests that stress occurring after viral exposure may increase susceptibility, whereas mixed findings (increased and decreased susceptibility) have been reported when stress occurs prior to viral exposure. Temporal relations clearly go uncontrolled in naturalistic studies, and are more difficult to determine, as no information is available about the timing of subjects' exposure to virus. Such temporal issues could be addressed in viral exposure trials. (2) *Little is known about differential effects of acute (shorter-term), chronic (longer-term), and repetitive stressors.* The health psychology literature suggests that chronic stress may have particularly pernicious effects on health, so distinctions among the duration and patterns of stress should be researched for their effects on URI. However, additional conceptual work may be needed to define stressors according to a chronicity dimension. (3) *True experimental studies of stress exposure should be conducted (namely, where subjects are randomly assigned to stressor conditions).* Although viral exposure studies appear to be experimental (because they have a high degree of experimenter control over the situation), as mentioned above, they generally are not because the independent variable, stress, is not manipulated. A number of experimental stress procedures have been developed and used extensively in cardiovascular reactivity and psychoendocrinology research. These procedures could easily be adapted for use in conjunction with viral exposure trials, and would increase confidence in the causal processes suggested by observational studies. (4) *Little is known about the biological pathways that may be responsible for the association between stress and URI.* We have outlined several points in the process from viral exposure through resulting protective memory response after the infection where stress could affect URI. As we noted above, very few of these have been researched. (5) *Biological mechanisms underlying associations between psychological stress and URI should be investigated in viral exposure studies.* Control over extraneous factors (e.g., smoking, alcohol consumption, exercise) that may affect URI can be controlled or at least adequately assessed in such studies, which should aid in the detection of mechanisms. (6) *The results obtained from the experimental, viral inoculation studies should be used as sources of hypotheses that can be tested in real world settings.* Although experimental infection studies lend themselves to the investigation of psychobiological mechanisms involved in URI, it is critical to establish their relevance outside the laboratory. As with studies of cardiovascular reactivity, it is important to demonstrate the clinical significance of laboratory results. Field studies will also be necessary to determine the relative importance of psychobiological relations in comparison to other risk factors in the community. (7) *The impact of psychosocial interventions designed to capitalize on results obtained from the experimental, viral inoculation studies should be assessed in real world settings.* The effectiveness of psychosocial interventions in ameliorating a number of health problems (e.g., cardiovascular disease, cancer) is increasingly being investigated. If an appropriate psychosocial intervention were found to result in reduced stress and reduced URI, one could make a compelling case for causal relationships in a field study. Such intervention studies would also be informative with regard to the public health significance of psychosocial effects in URI.

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Sources of Anticipatory Emotional Distress in Women Receiving Chemotherapy for Breast Cancer

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Summary

Background: The contribution of classical conditioning processes to patients' distress before chemotherapy infusions (anticipatory distress) was compared to other potential sources of distress (e.g., trait anxiety). We hypothesized that posttreatment distress (putative unconditioned response) would become a stronger predictor of anticipatory distress as patients underwent more treatment infusions (putative conditioning trials).

Materials and methods: Fifty women with early stage breast cancer, undergoing standard chemotherapy, completed questionnaires in the clinic prior to each of eight consecutive treatment infusions, as well as telephone interviews to assess side effects following infusions.

Results: Consistent with the conditioning hypothesis, posttreatment distress became significantly related to anticipatory distress at the fourth infusion and became the strongest predictor by the sixth. Path analysis indicated that posttreatment distress had a direct influence on anticipatory distress, and that trait anxiety had an indirect influence by influencing apprehension about chemotherapy which, in turn, directly predicted anticipatory distress.

Conclusions: The results of the present study contribute to an emerging view of anticipatory distress as a conditioned response in chemotherapy patients. Results demonstrate that conditioning factors may be one of the strongest predictors of anticipatory distress in the later phases of chemotherapy treatment.

Key Words: anticipatory distress, breast cancer, chemotherapy, classical conditioning

Background

Patients receiving chemotherapy for cancer experience considerable emotional distress, as documented in numerous clinical reports (1-5). Although many possible sources of distress have been examined in these studies, little attention has been paid to the possibility that these sources may vary with the timing of the assessment in relation to chemotherapy administration. In most previous studies, no distinction was made between distress experienced after treatment infusions (posttreatment distress) and distress experienced in the clinic before infusions (anticipatory distress). This distinction may have heuristic value because there may be different sources of distress during these two periods.

During the posttreatment period, patients may experience a variety of aversive side effects (e.g., pain, fatigue, nausea) (6). Considerable research suggests that patients who experience more side effects have higher levels of emotional distress during the posttreatment period (7,8). During the pretreatment period, however, distress may occur even in the absence of treatment side effects. Indeed, distress has been found to be most severe prior to patients' first infusion of chemotherapy (i.e., prior to any experience with chemotherapy) (5,9). High levels of distress prior to the first infusion of chemotherapy have been linked to trait anxiety, an individual's propensity to experience anxiety in threatening situations (10), as well as to patients' expectations of experiencing aversive side effects (9). At subsequent infusions, patients' prior experience of aversive side effects and emotional distress may also contribute to anticipatory distress. Based on their experiences of these aversive side effects, patients may become distressed due to their expectations of having similar reactions again. Patients' prior experiences of posttreatment distress may result in the development of classically conditioned distress at subsequent infusions.

The role of classical conditioning in the development of anticipatory reactions to chemotherapy has been most extensively studied with regard to anticipatory nausea and vomiting (ANV) (11). Numerous clinical studies indicate that ANV develops when the sights, smells, and sounds in the clinic environment (putative conditioned stimuli) are paired with the administration of chemotherapy (unconditioned stimulus) that elicits posttreatment nausea and vomiting (unconditioned response). After one or more pairings, exposure to these clinic cues alone (e.g., in the clinic, before chemotherapy is administered) is sufficient to elicit nausea and/or vomiting (conditioned response) (12-14).

Analogous to conditioned nausea and vomiting, conditioned emotional distress has been hypothesized to develop when clinic cues are paired with chemotherapy that elicits posttreatment emotional distress (putative unconditioned response) (2,5,9). To date, two lines of evidence support this hypothesis. First, consistent with the view that clinic cues function as conditioned stimuli, patients' distress levels have been found to increase markedly upon their return to the clinic environment where they had received treatment (5,15). Second, consistent with the view that posttreatment distress functions as an unconditioned response, the presence of distress after an infusion has been found to predict the occurrence of anticipatory distress at the next infusion, regardless of the number of other side effects reported (9). Although the results of these studies are consistent with a conditioning explanation, no study has yet examined the importance of conditioning, relative to other factors, in predicting the severity of anticipatory distress in chemotherapy patients.

The primary aim of the present study was to examine the contribution of patients' levels of posttreatment distress (intensity of the unconditioned response) to their subsequent levels of anticipatory distress. This contribution of posttreatment distress was statistically compared to that of the following nonconditioned sources of anticipatory distress: 1) proneness toward experiencing

anxiety in threatening situations (trait anxiety); 2) apprehension about chemotherapy (operationally defined as the level of emotional distress before the first infusion); and 3) the extent of aversive treatment-related symptomatology (total number of side effects other than emotional distress).

We hypothesized that posttreatment distress (putative unconditioned response) would be a more important predictor of anticipatory distress as patients underwent more treatment infusions (putative conditioning trials). We also hypothesized that the predictor variables would both directly and indirectly (by influencing one another) influence the intensity of patients' anticipatory distress.

Patients and Methods

Patients: Fifty women scheduled to receive intravenous adjuvant chemotherapy treatment for breast cancer who met the following criteria were included in the present sample: 1) diagnosed with Stage I or II breast cancer, status post radical, modified radical, or segmental mastectomy; 2) Karnofsky performance status over 70; 3) no previous chemotherapy treatment; 4) not scheduled to receive radiation during the course of chemotherapy; 5) 18 years of age or older; 6) not currently pregnant; 7) no current or previous neurological or psychiatric disorders; 8) no concurrent serious illness; 9) English speaking; 10) no hearing impairment; 11) not scheduled for oral chemotherapy; and 12) complete data collected for eight infusions. Patients ranged in age from 28 to 74 years with a mean age of 48 years (s.d. = 10.3). The sample was predominately white (82%), married (69.4%), and well-educated, with 59% having at least a college degree. Most women (56.2%) were working at the start of chemotherapy, while 23% were not working (students, retirees, homemakers) and 20.8% were on leave from employment.

A review of patients' medical records indicated that they were treated with the following standard combinations of chemotherapy agents: (1) CMF (cyclophosphamide [C] [600 mg/M^2], methotrexate

[M] [40 mg/M^2], and 5-fluorouracil [F] [600 mg/M^2]) I.V. q 21/28 d (n = 38); (2) Adriamycin (75 mg/M^2) I.V. q 21 d followed by CMF as above (n = 10); (3) Adriamycin (75 mg/M^2) I.V. q 21 d (n = 1); or (4) CMF as above followed by CAF (C [500 mg/M^2], adriamycin [50 mg/M^2], and F [600 mg/M^2]) I.V. q 28 d (n = 1). Patients received a standard regimen of I.V. antiemetic medications at each infusion, including dexamethasone (10 - 40 mg) and lorazepam (0.5 - 2.0 mg). This regimen was modified as clinically necessary on an individual basis by each patient's attending oncologist with one or more of the following: prochlorperazine (10 mg), metoclopramide hydrochloride (40 - 100 mg), ondansetron (0.15 mg/kg), or diphenhydramine hydrochloride (25 - 50 mg). Repeated measures analysis of variance revealed that antiemetic doses did not vary over the course of treatment (p's $\geq$.26).

Data for this study were drawn from an ongoing investigation of psychological and biological reactions to cancer chemotherapy. Previous reports from this continuing project have focused on the development of conditioned nausea (16) and the formation of aversions to normal dietary items (17) during the course of chemotherapy treatment. None of the subjects included in the present study was included in the three previously published studies that included assessments of anticipatory distress (5,9,15).

Methods

As in our previous research, patients completed study measures (described in detail below) in the clinic waiting area before each treatment infusion. Patients were also contacted by telephone four to seven days after each infusion to assess the presence of chemotherapy-related side effects, including distress (see below). In addition, patients completed a demographic data form and a measure of trait anxiety.

Trait Anxiety: Patients completed the Taylor Manifest Anxiety Scale (TMAS) (18) at home between their second and third chemotherapy infusions. Because trait anxiety, as measured by the TMAS, has been demonstrated to be a stable trait (three-week test-retest reliability, $r = .89$; five-month test-retest reliability, $r = .82$ (18)), patients completed this questionnaire at home to reduce the time required for clinic assessments.

Pretreatment assessments: During each pretreatment infusion assessment, patients reported the intensity of emotional upset and nausea on 10-centimeter visual analog scales (VAS), as previously described (16). Separate VAS for emotional upset and nausea were completed for the following time points: last night; this morning; and right now. Data from these time points were combined (mean) with the measure of distress in the treatment room (see below) to define patients' levels of anticipatory distress based on evidence indicating high intercorrelations ($r = .21$ to $.96$).

Posttreatment assessments: During each posttreatment infusion telephone assessment, patients were asked to report on the presence or absence of 12 common side effects, as previously described (16). Patients also reported the intensity of posttreatment emotional upset and nausea (0-100) in the 24 hours after chemotherapy administration and provided a retrospective assessment of the presence and intensity (0-100) of emotional upset and nausea in the treatment room immediately before chemotherapy administration. The side effects assessed were: chills, sleep problems, diarrhea, weakness, fatigue, hair loss, vomiting, taste change, change in appetite, skin itching, and pain.

This study was designed to test two hypotheses. First, we predicted that posttreatment distress (putative unconditioned response) would become a more important predictor of subsequent anticipatory distress as patients received more chemotherapy infusions (putative conditioning trials). To test this hypothesis, we conducted a series of stepwise multiple regression analyses to examine

the contribution of each of the predictor variables to the intensity of patients' anticipatory distress at the second through the eighth infusions. Second, we proposed that some predictor variables might have an indirect influence on anticipatory distress through their effects on more proximal variables. Specifically, we hypothesized that trait anxiety might influence patients' apprehension about chemotherapy (distress before infusion one), which, in turn, might influence subsequent anticipatory distress. Similarly, distress before infusion one might influence both posttreatment distress and the number of posttreatment side effects. Each of these variables, in turn, might independently influence subsequent anticipatory distress. Our proposed causal model is graphically depicted in Figure 1. To explore these proposed causal relations among the variables under study, we performed a path analysis (19) of the sources of anticipatory distress at the eighth infusion.

Results

Anticipatory Distress: Distress levels assessed during the pretreatment period were highest before the first infusion 36.8 $\pm$ 26.7 (mean $\pm$ s.d.), and ranged from 24.2 $\pm$ 21.5 to 30.2 $\pm$ 24.3 across subsequent infusions. At each infusion, the vast majority of women (ranging from 94 - 100%) had some anticipatory distress (i.e., > 0).

Predictors of Anticipatory Distress Across Infusions: Preliminary analyses were conducted to determine whether demographic variables (i.e., age, race, education, marital status, employment status) were related to patients' distress levels prior to treatment infusions. The only variable found to be associated with anticipatory distress was age, which was correlated at only one of the eight infusions. Confirming the importance of trait anxiety as a predictor of distress before the first treatment infusion (9), a significant correlation was found between these two variables ($r = .53$, $p = .001$).

To examine the sources of anticipatory distress across subsequent infusions (i.e., infusions 2 - 8), separate stepwise multiple regression equations were computed to identify which variables were related to the intensity of anticipatory distress before each infusion. Four variables previously reported to be related to anticipatory distress (trait anxiety, distress intensity before the first infusion, number of posttreatment side effects after the prior infusion, and level of posttreatment distress after the prior infusion) were included as predictors in these analyses. Following stepwise procedures, the predictor accounting for the most variability in anticipatory distress scores was allowed to enter each analysis on the first step, followed by the predictor accounting for the most remaining variability on step 2, and so on, until no remaining variable made a significant ($p \leq .05$) contribution. Thus, the variable identified in step 1 (see Table) is the strongest predictor of anticipatory distress (i.e., accounted for the most variability) and is followed by the variables accounting for the most remaining variability on subsequent steps.

Consistent with the conditioning hypothesis, posttreatment distress (putative unconditioned response) was significantly related to anticipatory distress at the fourth infusion and became the strongest predictor by the sixth infusion (see Table). Distress before infusion one (apprehension about chemotherapy) was the strongest predictor of anticipatory distress before infusion two, and remained significant at all subsequent infusions. The number of posttreatment side effects was a significant predictor at only two infusions (three and five). Trait anxiety was not a significant predictor at any infusion after the first.

<REM> PLEASE INSERT TABLE ABOUT HERE <REM\>

Analysis of Direct and Indirect Predictors of Anticipatory Distress: Although the previous results indicate that posttreatment distress is the strongest predictor of anticipatory distress at infusions six through eight, the stepwise regression approach does not address the possibility that the predictors

may have both direct and indirect relations with anticipatory distress. Direct relations would be evident if the predictor accounted for variability in anticipatory distress independent of other predictors. Indirect relations would be evident if the predictor accounted for variability in other predictors which, in turn, had direct relations with anticipatory distress. To examine the direct and indirect relations between the predictor variables and anticipatory distress before the eighth infusion, we conducted a classic path analysis (19). This analysis tested the existence of the proposed paths relating the predictor variables to each other and to anticipatory distress and estimated their associative strength.

The model and path coefficients are presented in the Figure. Trait anxiety was found to be neither directly related to anticipatory distress nor indirectly related via posttreatment side effects or posttreatment distress. However, trait anxiety did have an indirect effect on anticipatory distress through its influence on anxiety before infusion one. Patients higher in trait anxiety reported higher distress before the first infusion, and as shown in the Figure, distress before the first infusion had a direct effect on anticipatory distress. Consistent with the conditioning hypothesis, posttreatment distress was also directly related to anticipatory distress, such that higher levels of posttreatment distress were predictive of greater anticipatory distress.

<REM> PLEASE INSERT FIGURE ABOUT HERE <REM\>

Although the stepwise regression and the path analysis suggest that posttreatment distress accounts for significant variability in anticipatory distress, it is important to consider the possibility that this effect may have reflected the shared variance of posttreatment distress and posttreatment side effects, which were significantly correlated ($p < .001$). In order to confirm the unique contribution of posttreatment distress after infusion seven to anticipatory distress at infusion eight we conducted one additional regression analysis. Using a hierarchical approach, we entered all other

predictors (i.e., trait anxiety, distress before the first infusion, and posttreatment side effects) before examining the unique contribution of posttreatment distress to anticipatory distress. Results indicated that posttreatment distress accounted for additional significant variability in anticipatory distress even after accounting for the variability attributed to all the other predictors ($p < .01$).

Relation between Anticipatory Distress and Anticipatory Nausea: It is conceivable that anticipatory distress could, at least in part, be secondary to anticipatory nausea. However, in this study the incidence of anticipatory distress (> 90% at every infusion) was considerably higher than that of anticipatory nausea, which ranged from 6% to 36% across infusions. Thus, the vast majority of women reporting distress did not report concurrent anticipatory nausea. Moreover, including anticipatory nausea intensity at infusion 8 as a predictor in the stepwise regression described above did not alter the results. Posttreatment distress remained the strongest predictor, while anticipatory nausea intensity was not significantly related ($p = .50$) to anticipatory distress.

Conclusions

In this study, we sought to examine the relative importance of several predictors of anticipatory distress in women receiving chemotherapy for breast cancer. The results of this study indicate that the predictors of anticipatory distress vary over the course of repeated infusions of chemotherapy, with classical conditioning factors being most strongly related at later infusions. In the discussion that follows, we summarize the results and consider each in relation to the literature. We then consider the clinical implications of these results and discuss the potential utility of clinical interventions to alleviate anticipatory emotional distress in patients receiving chemotherapy treatment.

The present study provides two new lines of evidence supporting the view that conditioning processes contribute to anticipatory distress in patients receiving chemotherapy for cancer. First, the relative importance of a conditioning variable as a predictor of patients' experiences of anticipatory distress was demonstrated. Consistent with its hypothesized role as an unconditioned response, we found that the intensity of patients' posttreatment distress became significantly related to anticipatory distress by the fourth infusion and became the strongest predictor of anticipatory distress by the sixth. Second, a direct relation between posttreatment distress and anticipatory distress was established by use of a path analysis. Furthermore, a hierarchical regression analysis confirmed that after statistically controlling for the contribution of all other predictors, the relations between posttreatment distress and subsequent anticipatory distress remained significant.

Three additional sets of findings indicated that anticipatory distress may also have a nonconditioned component. First, patients' levels of trait anxiety were directly related to anticipatory distress before only the first infusion. The path analysis indicated, however, that trait anxiety may have an indirect effect on subsequent anticipatory distress through its influence on patients' apprehension about chemotherapy before they have any personal experience of it (operationally defined as distress before infusion one). Second, patients' apprehension about chemotherapy significantly contributed to the intensity of their anticipatory distress at every infusion. The direct influence of patients' apprehension was confirmed by the path analysis. Third, the number of posttreatment side effects predicted patients' anticipatory distress levels at infusions three and five. Patients who experienced more posttreatment side effects were more likely to experience anticipatory distress at these infusions. This relation may reflect patients' cognitive expectations of aversive side effects based on past experience. However, it is not yet clear why this relation may be stronger at some infusions than at others.

The results of the present study support and extend three previous reports (5,9,15), which are consistent with the view that classical conditioning processes contribute to patients' levels of anticipatory distress before chemotherapy infusions. Extending the findings of these studies, the present study is the first to demonstrate the relative importance of posttreatment distress (putative unconditioned response) as a predictor of anticipatory distress. Indeed, we found that the intensity of posttreatment distress was the strongest predictor of anticipatory distress at infusions later in the course of treatment. Moreover, the path analysis indicated that the intensity of patients' posttreatment distress was directly related to their anticipatory distress prior to the eighth infusion, and the hierarchical regression further confirmed that this relation was independent of the other predictors. One must, however, be cognizant of the potential for unexamined confounding variables inherent in clinical studies such as these. In the absence of experimental verification, one cannot accept the conditioning hypothesis without reservation.

Further support for the conditioning hypothesis comes from a recent study that employed an experimental model of conditioned distress in chemotherapy patients (20). In this experimental study, patients were randomly assigned to either have presentation of a distinctive beverage systematically paired with chemotherapy administration or not. After several such pairings, the beverage was presented to patients in their homes (in the absence of clinic cues or impending chemotherapy). Patients in the experimental group (who had previously had the beverage paired with chemotherapy infusions) had increased levels of distress after the beverage presentation. Control patients (who had never received the beverage in conjunction with treatment) did not. This experimental study provides compelling evidence that patients can develop a conditioned distress response to a cue explicitly paired with chemotherapy. Complementing these results, the present study suggests that anticipatory distress before chemotherapy infusions represents a conditioned response to ordinary clinic cues.

Consistent with the literature on anticipatory nausea (21,22), the present study suggests that multiple conditioning trials (i.e., chemotherapy infusions) may be necessary before the conditioned component of anticipatory distress is detectable. The need for multiple conditioning trials in the development of conditioned anticipatory distress is consistent with neo-conditioning theory (23), which postulates that the strength of an acquired fear reaction is determined by the number of times there is an association between the conditioned stimulus and the unconditioned response.

In the present study, as in a previous study (9), trait anxiety was found to be related to the intensity of patients' distress before the first infusion of chemotherapy. Interestingly, we found that following experience with chemotherapy treatment, patients' levels of trait anxiety were no longer predictive of their subsequent anticipatory distress. Indeed, the path analysis at infusion eight confirmed that trait anxiety was not directly related to the intensity of anticipatory distress, although it was indirectly related through its influence on patients' apprehension about chemotherapy. These results are consistent with the view that the effects of trait anxiety may be more pronounced with novel stressors (24).

Consistent with our prior research (9), patients who had higher levels of distress before their first infusion of chemotherapy reported greater anticipatory distress before all subsequent infusions. Although distress before the first infusion is clearly a powerful predictor of subsequent anticipatory distress, the sources of such apprehension about chemotherapy remain to be determined. In addition to trait anxiety, a myriad of psychosocial and treatment-related factors could play a role. For example, it is likely that patients have expectations about the aversiveness of chemotherapy based on reports from family, friends, the media, and/or medical personnel. Additionally, patients' apprehension may be based on prior unpleasant experiences with medical procedures, such as biopsy and surgery. Alternatively, distress before patients' first infusion of chemotherapy may be, in part, a conditioned response. Analogous to "white coat hypertension" (25), patients may have

formed conditioned distress responses to medical clinics due to previous anxiety-provoking interactions. Finally, one must also consider possible external sources of distress, including hassles associated with treatment visits (e.g., traveling to the clinic, arranging for child care, taking time off from work). These potential sources of distress should be examined in future research.

Contrary to our previous research (9), the number of side effects patients experienced after an infusion was not related to the subsequent intensity of anticipatory distress at all infusions. The apparently less robust finding in this study could reflect differences in the statistical analyses performed. The previous study forced this variable into hierarchical regression analyses prior to the posttreatment distress variable (putative unconditioned response), such that any shared variance of side effects with posttreatment distress would be attributed only to the number of side effects experienced. In the present study, we examined the relative influence of each variable in stepwise regressions, which enter the variable that accounts for the most variance on the first step; shared variance with other predictors would thus be attributed to that variable ("winner takes all" approach). It should be noted that in both studies, the influence of side effects may have been underestimated because of the methodological constraints of the measure. Simply counting the number of side effects results in a variable with a limited range, which reduces the likelihood of finding significant effects. It is possible that patients' ratings of the intensity of side effects would be a better predictor of their levels of anticipatory distress. Although we assumed that patients' negative expectations of side effects are the result of their previous experience of side effects, the nature of this relation was not established in the present study. Perhaps assessments of patients' actual expectations would be more predictive of anticipatory distress. However, contrary to this possibility, a previous study (9) has shown that patients' expectations of side effects (at least when assessed prior to the start of treatment) are not related to subsequent anticipatory distress. Future researchers should thus consider directly assessing patients' expectations of side effects prior to each chemotherapy infusion.

It is important to note that the present study did not examine a multitude of psychosocial factors that could modify patients' levels of distress. For example, patients who respond to their cancer diagnoses and treatments by employing certain coping processes (e.g., escape-avoidance) have been found to have more emotional distress (26-28). Another psychosocial factor that might influence distress levels is social support. Research has demonstrated that women with a chronic medical condition have higher levels of distress when they receive negative support from their husbands (29). It seems unlikely that the inclusion of these psychosocial factors would have affected the significant relation between posttreatment distress and anticipatory distress in the present study. However, in future examinations of these factors, investigators may wish to consider their influence within a conditioning framework.

More than 90% of patients in the present sample reported distress before each infusion. Results from the present study indicate the importance of conditioning to this anticipatory distress and suggest ways in which interventions based on conditioning principles could be therapeutic. For example, reducing posttreatment distress (putative unconditioned response) should reduce subsequent (conditioned) anticipatory distress. Reduction of posttreatment distress could be accomplished in at least two ways. First, pharmacologic agents (e.g., anxiolytics) taken after chemotherapy infusions might be used to substantially reduce posttreatment distress. Behavioral interventions, such as relaxation training, could also be implemented to decrease emotional distress. Support for this possibility can be found in the literature on anticipatory nausea and vomiting in cancer patients. Chemotherapy patients trained to use relaxation techniques to control nausea experienced less posttreatment nausea and were also less likely to develop anticipatory nausea (30,31). Further research is needed to assess the efficacy of such interventions in reducing or preventing conditioned emotional distress in chemotherapy patients.

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Table 1: Significant Predictors of Anticipatory Distress at Infusions 2-8

	Infusion 2	Infusion 3	Infusion 4	Infusion 5	Infusion 6	Infusion 7	Infusion 8
Step 1	Distress Before Infusion 1 $R^2 = .44^{***}$	Posttreatment Side Effects $R^2 = .19^{**}$	Posttreatment Distress $R^2 = .37^{***}$	Distress Before Infusion 1 $R^2 = .30^{***}$	Posttreatment Distress $R^2 = .41^{***}$	Posttreatment Distress $R^2 = .24^{***}$	Posttreatment Distress $R^2 = .34^{***}$
Step 2		Distress Before Infusion 1 $R^2 = .07^{*}$	Distress Before Infusion 1 $R^2 = .11^{**}$	Posttreatment Distress $R^2 = .11^{**}$	Distress Before Infusion 1 $R^2 = .16^{***}$	Distress Before Infusion 1 $R^2 = .08^{*}$	Distress Before Infusion 1 $R^2 = .13^{**}$
Step 3				Posttreatment Side Effects $R^2 = .05^{*}$			

* $p < .05$

** $p < .01$

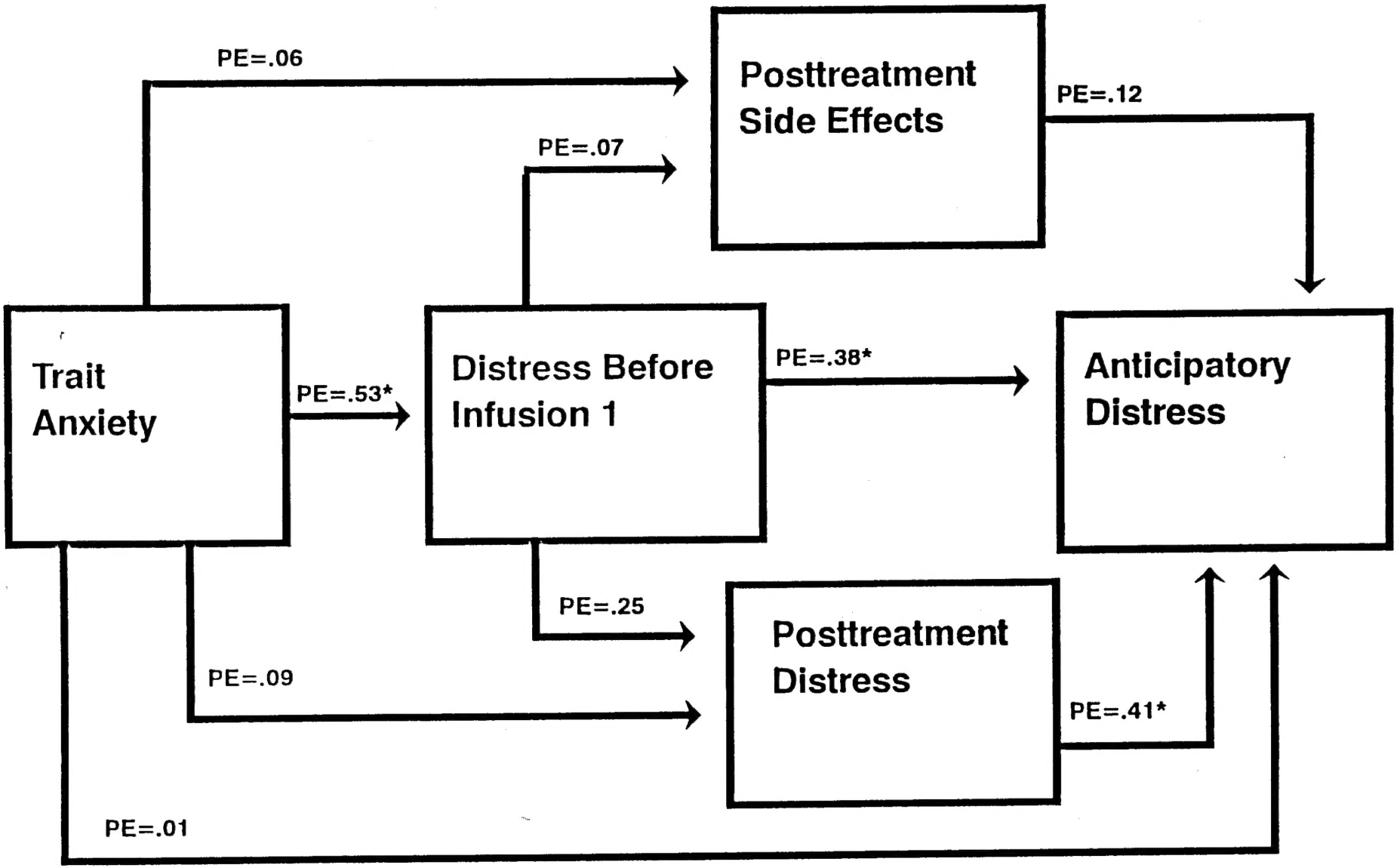
*** $p < .001$

Figure Legend

Figure 1: Path Analysis of Anticipatory Distress before Infusion 8.

*$p < .05$

PE = parameter estimate


PE=.06
Posttreatment Side Effects
PE=.12
PE=.07
Trait Anxiety
PE=.53*
Distress Before Infusion 1
PE=.38*
Anticipatory Distress
PE=.25
Posttreatment Distress
PE=.09
PE=.41*
PE=.01